II. Remarks

A. Status of the Claims

Claims 1, 97-98, 102, 115, 127 and 129 are amended. Claims 2-4, 10, 29-83, 99-101, 113-114, and 126 are cancelled. Claims 1, 5-9, 11-28, 84-98, 102-112, 115-125, and 127-129 are pending.

B. Support for Amended Claim Language

Support for amended claim language is found throughout the specification. In particular, support for "mutation" is found throughout paragraph [0011] on page 3, lines 9-19, for example. Support for language "with reference to wild-type M-MLV" is found in the specification at Example 3, page 23, lines 2-3 that state: "For example, to create the F155Y; H638G MMLV RT mutant, the following changes to the RT gene were made, *beginning with wild-type MMLV RT* (Accession number J02255)... ." Emphasis added. Applicants submit that no new matter has been introduced by the amended claim language or the added claim language.

C. Claim Objections

Claim 1 has been amended to include the full name of M-MLV as required by the Office Action at page 2.

D. Rejection of Claims under 35 U.S.C. §112, Second Paragraph

Office Action

The Office Action states a rejection of Claims 1, 5-9, 11-28, 84-98, 102-112, 115-125 and 127-129 as indefinite for lacking reference to an amino acid sequence. Office Action at page 3.

Response

Applicants traverse this rejection. Claim 129, as amended, recites "An isolated reverse transcriptase protein comprising SEQ ID NO:2." SEQ ID NO:2 is an amino acid sequence. Claim 129, therefore, is improperly included in this rejection. Applicants respectfully request that the rejection of Claim 129 under 35 U.S.C. §112, second paragraph, be withdrawn.

Independent Claims 1, 97, 98, 102, 115, and 127 have been amended to recite that the mutations are in reference to wild-type M-MLV. One of skill in the art realizes that the N-terminal methionine residue may or may not be present in a protein sequence; similarly, leader sequences may or may not be present thereby affecting the numbering of each amino acid in a protein sequence. One of ordinary skill in the art would readily recognize mutation locations H638 and F155 by reference to a wild type sequence. The specification teaches such a wild-type sequence in citing Accession No. J02255 in working Example 3; see the specification at page 23, lines 2-3. Applicant submits that amended independent Claims 1, 97, 98, 102, 115, and 127 therefore are not indefinite.

An essential characteristic of a proper dependent claim is that it shall include every limitation of the claim from which it depends. Therefore, a dependent claim is allowable when the claim from which it depends is allowable. Claims 5-9, 11-28, 84-96, 103-112, 116-125, and 128 are directly or indirectly dependent upon Claims 1, 97, 98, 102, 115, or 127. Therefore, Applicants submit that said claims are not indefinite and respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

E. Rejection of Claims under 35 U.S.C. §112, First Paragraph

Office Action

The Office Action states a rejection of Claims 1, 5-9, 11-28, 84-98, 102-112, 115-125 and 127-129 for not limiting the claimed transcriptase mutants structurally and thus failing to meet the written description and enablement requirements of 35 U.S.C. §112. Office Action at pages 2-8.

Response

Applicants traverse these rejections.

Regarding the Written Description rejection:

The text of *Capon v. Eshhar* 76 USPQ2d 1078 decided by the Federal Circuit August 12, 2005 states at page 1085: "the "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."

In addition, at page 1084, the *Capon v Eshhar* decision cited *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003) stating that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure."

In *Falkner v. Inglis* 79 USPQ2d 1001 (Fed. Cir. 2006), the Court specifically held, at 1007, in accordance with prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

The amino acid sequence of Moloney Murine Leukemia Virus reverse transcriptase protein is known (See Shinnick, T. M., *et al.*; "Nucleotide sequence of Moloney murine leukemia virus" *Nature* 293 (1981) 543-548 cited in U.S. Patent No. 5,017,492, which patent is cited on page 2 of the present specification, line 10, and also in the Information Disclosure Statement filed May 15, 2006).

Further, the reverse transcriptase gene may be obtained from public sources, e.g., ATCC, or may even be purified from eukaryotic cells infected with a retrovirus, or from a plasmid that includes a portion the retrovirus genome that includes the RT (see the present specification, page 18, lines 17-19).

The present specification also cites the Accession No. for the wild type M-MLV RT sequence as J02255 (working Example 3 at page 23, lines 2-3).

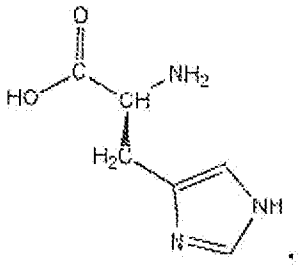
U.S. Patent 6,136,582 describes a reverse transcriptase of M-MLV having a substitution of valine at position 155.

Therefore, the structures of the reverse transcriptase of M-MLV and at least one mutant thereof are known to one of ordinary skill in the art.

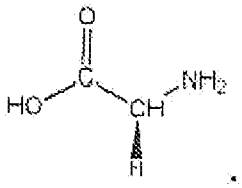
The present specification has defined the processivity domain as generally corresponding to amino acids 497 to 671 of M-MLV reverse transcriptase (specification at page 3, lines 3-4). This region includes 175 amino acids.

Independent Claim 1 is to an isolated hyperactive M-MLV reverse transcriptase protein having a mutation at Histidine-638 with reference to wild type M-MLV. Therefore, of the 175

amino acids in the processivity domain, Applicants identified the replacement of histidine at position 638 as providing the hyperactivity claimed. Histidine has the structure:



In particular, Applicants replaced the histidine at position 638 with glycine. Glycine has the structure:



As can be seen by one of ordinary skill in the art, replacement of histidine with glycine effectively removes the side chain imidazole ring at position 638. As is also known by one of ordinary skill in the art, an imidazole ring can switch between uncharged or positively charged states depending on its local environment.

Since there are 20 naturally occurring amino acids, a mutation of the histidine corresponding to position 638 can yield, at most, one of 19 other amino acids at that position. None of the other 19 amino acids contains an imidazole ring side chain. Therefore, the genus of reverse transcriptases contains, with regard to position 638, at most, 19 members and none of the 19 replacement amino acids contain an imidazole ring. Applicants submit that all 19 members of the genus of reverse transcriptases with reference to position 638 are adequately described.

A mutation at position F155 is known in the art (U.S. Patent 6,136,582 cited by the Office Action). The genus of claimed reverse transcriptases set forth by Claim 1 contains, at most, 19 members with respect to position 155.

Therefore, the number of members of the genus containing F155 and H638 mutation combinations is 19 X 19 or 361 combinations. Applicants submit that each combination can be

written out using the wild type sequence of M-MLV and replacing the histidine-638 with one of each of 19 amino acids and replacing the phenylalanine-155 with one of each of 19 amino acids. Applicants therefore submit that the invention as set forth by Claim 1 is fully described by the specification in light of knowledge of one of ordinary skill in the art.

Independent Claims 97, 98, 102, 115, and 127 recite a hyperactive reverse transcriptase protein comprising H638G with reference to wild-type M-MLV. Said independent claims therefore set forth one member of the genus of mutations at the histidine-638 position; specifically, the mutation in which position 638 is a glycine. At page 18, the specification states:

> The reverse transcriptase gene (or the genetic information contained therein) can be obtained from a number of different sources, e.g., Moloney Murine leukemia virus (M-MLV); human T-cell leukemia virus type 1 (HTLV-I); bovine leukemia virus (BLV); Rous Sarcoma Virus (RSV); human immunodeficiency virus (HIV); yeast, including Saccharomyces, Neurospora, Drosophila; primates; and rodents. See, e.g., Weiss et al., U.S. Pat. No. 4,663,290 (1987); Gerard, G. R., DNA 5:271-279 (1986); Kotewicz, M. L., et al., Gene 25:249-258 (1985); Tanese, N., et al., Proc. Natl. Acad. Sci. (USA) 82:4944-4948 (1985); Roth, M. J., et al., J. Biol. Chem. 260:9326-9335 (1985); Michel, F., et al., Nature 316:641-643 (1985); Akins, R. A., et al., Cell 47:505-516 (1986), EMBO J. 4:1267-1275 (1985); and Fawcett, D. F., Cell 47:1007-1015 (1986). For instance, the gene may be obtained from public sources, e.g., ATCC, or may even be purified from eukaryotic cells infected with a retrovirus, or from a plasmid that includes a portion the retrovirus genome that includes the RT.

In light of the known reverse transcriptases cited above and in reference to the sequence structure of M-MLV, the invention as set forth by independent claims 97, 98, 102, 115 and 127 is fully described by the specification.

For these reasons and in light of the *Capon v. Eshhar*, *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, and *Falkner v. Inglis* Federal Circuit decisions cited above, Applicants submit that the invention as set forth by independent Claims 1, 97, 98, 102, 115, and 127 is adequately described in the specification.

An essential characteristic of a proper dependent claim is that it shall include every limitation of the claim from which it depends. Therefore, a dependent claim is allowable when the claim from which it depends is allowable. Claims 5-9, 11-28, 84-96, 103-112, 116-125, and 128 are directly or indirectly dependent upon Claims 1, 97, 98, 102, 115, or 127. Therefore,

Applicants submit that said claims are not indefinite and respectfully request that the rejection under 35 U.S.C. §112, first paragraph, regarding written description, be withdrawn.

Claim 129 has been amended to recite the protein of SEQ ID NO:2. Applicants therefore respectfully request that the written description rejection of Claim 129 under 35 U.S.C. §112 be withdrawn.

Regarding the Enablement rejection:

Enablement is a question of law involving underlying factual inquiries. See *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (42 USPQ2d 1001) (Fed. Cir. 1997); see also *In re Wands*, 858 F.2d 731, 737 (8 USPQ2d 1400) (Fed. Cir. 1988) (holding that whether undue experimentation is required is a "conclusion reached by weighing many factual considerations... including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.").

Independent Claim 1 is to, in part, a hyperactive Moloney Murine Leukemia Virus reverse transcriptase protein having a mutation at Histidine-638 with reference to wild type M-MLV. The specification states at Example 1, page 20, lines 24-25: "As MMLV RT is modified easily by molecular techniques, this enzyme was the target for improvement efforts."

Independent Claims 97, 98, 102, 115, 127 and 129 are to, in part, a hyperactive reverse transcriptase protein having a mutation at Histidine-638 with reference to wild type M-MLV.

As cited above, page 18 of the specification describes various sources for the reverse transcriptase gene or the genetic information contained therein.

Applicants have described how to construct mutants using mutagenic primers (see Example 1 and Table 1, for example), how to express and purify mutant reverse transcriptases (see Example 4, for example), how to measure RNase H activity of mutant reverse transcriptases (see Example 5, for example), how to analyze cDNA products thereof (see Example 6, for example), and how to use the mutant reverse transcriptases in RNA amplification. Therefore, the tools and methods are provided for constructing a mutation at position H638 of reverse

transcriptase with reference to the wild-type M-MLV and the quantity of further experimentation for constructing such a mutant protein is not undue.

The nature of the invention is that of reverse transcriptase structure and function, a relatively mature technology in that the tools are available for study and much is known about the structure and function of wild-type enzymes.

It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt*, 537 F.2d 498, 504 (190 USPQ 214) (CCPA 1976). Applicants have taught how to make and use a hyperactive reverse transciptase having a mutation at H638. The mutation effectively removes an imidazole side chain from that location of the protein as stated above.

According to *KSR International Co. v. Teleflex Inc.* 127 S. Ct. 1727, April 30, 2007, at page 1742, a person of ordinary skill is a person of ordinary creativity.

Regarding the predictability or unpredictability of the art, Applicants note that although there is a vast amount of knowledge about reverse transcriptase structure and function in general, the structure and function of mutant proteins are still largely empirical, and there is often great difficulty in predicting precisely how a given mutant protein will behave. For that reason, the claimed invention cites particular locations of mutations in the processivity domain of reverse transcriptase demonstrated to provide a hyperactive reverse transcriptase.

Applicants submit that one of skill in the art is taught by the specification how to make and use the invention as set forth by the claims since, while certain experimentation would need to be carried out, such experimentation is not undue and is well within the skill of one in the art.

In light of these teachings, including the working examples, one of ordinary skill in the art could readily construct each of the 361 mutant reverse transcriptases that have a mutation at H638 and a mutation at F155 as set forth by independent Claim 1. Similarly, in light of these teachings, including the working examples, one of ordinary skill in the art could readily construct each of 19 mutant reverse transcriptases that have a mutation at H638 with reference to wild-type M-MLV as set forth by independent Claims 97, 98, 102, 115, 127, and 129.

An essential characteristic of a proper dependent claim is that it shall include every limitation of the claim from which it depends. Therefore, a dependent claim is allowable when

the claim from which it depends is allowable. Claims 5-9, 11-28, 84-96, 103-112, 116-125, and 128 are directly or indirectly dependent upon Claims 1, 97, 98, 102, 115, or 127. Therefore, Applicants submit that said claims are not indefinite and respectfully request that the rejection under 35 U.S.C. §112, first paragraph, regarding enablement, be withdrawn.

F. Rejection of Claim 129 under 35 U.S.C. § 102(b)

Claim 129 was rejected as anticipated by Gao *et al.* U.S. Patent No. 6,136,582.

Response

To anticipate a claim, each and every element of the claim must be found in a single prior art reference. MPEP § 2131.

Claim 129 recites "An isolated reverse transcriptase protein comprising SEQ ID NO:2." As stated by the figure legend for FIG. 3, SEQ ID NO:2 provides the protein sequence of F155Y;H638G MMLV RT. Gao *et al.* do not teach or suggest a mutation at amino acid 638. Therefore, Gao *et al.* cannot anticipate Claim 129.

Applicants respectfully request withdrawal of the rejection over Gao *et al.*

G. Conclusion

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request reconsideration of the claimed invention.

Should there be any questions or comments regarding this document, the Examiner is invited to contact Applicants' representative, Gloria L. Norberg at 512-721-3654 for discussion.

Respectfully submitted,

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